TLR4 signaling and tolerance: Dynamic knowledge representation using BioNetGen

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Intracellular pathways are generally displayed in static diagrams; in reality they exist with dynamic behavioral complexity. There is a need to develop means of "dynamic knowledge representation," where static conceptual models can be "brought to life" to demonstrate the mechanistic consequences intrinsic to such a model. BioNetGen is a rule-based software package intended to facilitate this process. This paper will present an example of dynamic knowledge representation of the Toll-like receptor 4 (TLR4) signaling pathway using BioNetGen, demonstrating adaptive preconditioning, otherwise known as "tolerance," to repeated exposure of lipopolysaccharide (LPS).

***Keywords* — knowledge representation, mathematical model, toll-like receptor, tolerance. Preconditioning, sepsis**

I. Purpose

Conceptual models representing the "knowledge" extracted from and communicated in the biomedical literature are generally represented in static diagrams. These depictions do not show all of the consequences of the actions they purport to represent. Thus, the verification of conceptual models represented in this fashion is possible only via indirect methods of additional experiment, observation and assumption. Being able to "bring these diagrams to life" in a dynamic fashion can be beneficial in the verification of conceptual models, such that the consequences of represented actions and interactions can be seen and evaluated. The utility of this approach will be demonstrated by examining the behavior and regulation of the toll-like receptor 4 (TLR4) signaling pathway, specifically the development of "tolerant" preconditioned states following repeat stimulus of the pathway.

II. Methods and Results

BioNetGen (BNG) is a rule-based modeling system that uses graphs to represent molecules, molecular complexes and their interactions [1]. While BNG was originally designed for detailed modeling of protein-protein interactions using a modular approach to model multiple active binding/interaction sites across different molecular species, in this paper BNG is utilized as a dynamic knowledge visualization tool. The interactions of TLR4 signaling are represented by state transition rules from one set of reactants to the next.

A. Methods

A series of review articles were surveyed concerning TLR4 signaling and modulation [2-5]. A selective representation of the TLR4 pathway was translated into a BNG model using its graphical interface RuleBuilder. Selection criteria for incorporated components included: 1) recognition as "canonical" components, such as the CD14/MD2/TLR4 complex 2) control loops with explicit causal descriptions in the literature and 3) inhibitory compounds with described causal generative pathways.

Experiments consisted of determining dose response of signaling output Tumor Necrosis Factor (TNF) to increasing doses of lipopolysaccharide (LPS). Next, pre-conditioning behavior was evaluated by re-dosing the model after an initial "priming" dose of LPS.

B. Results

The model demonstrated anticipated dose-dependent TNF response to perturbations with increasing levels of LPS at 10, 100, 1000 and 10000. The model also demonstrated "tolerance," evidenced by dose-dependent preconditioning with respect to degree of attenuation of TNF production upon secondary exposure to LPS.

III. Conclusion

We present a BNG model of TLR4 signaling and tolerance that reproduces the dynamical behavioral reported in the literature. The model also demonstrates the flexibility of BNG as a tool for dynamic knowledge representation. The modular nature of the model will allow the expansion of certain components of the pathway as more mechanistic detail becomes available.

Reference

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